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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 66.2(a)(ii) Rec'd PCT/PTO 23 MAR 2005



10/528674

Applicant's or agent's file reference Case 21406		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 03/10572	International filing date (day/month/year) 23.09.2003	Priority date (day/month/year) 27.09.2002	
International Patent Classification (IPC) or both national classification and IPC C07K14/21			
Applicant DSM IP ASSETS B.V. et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
 - ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application

Date of submission of the demand 09.03.2004	Date of completion of this report 22.12.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Kools, P Telephone No. +31 70 340-1964 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP 03/10572

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-18 as originally filed

Claims, Numbers

1-9 received on 03.08.2004 with letter of 02.08.2004

Drawings, Sheets

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
☒ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

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International application No. **PCT/EP 03/10572**

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-9
	No: Claims	
Inventive step (IS)	Yes: Claims	1-9
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-9
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item I

Basis of the report

The present IPER is based on an amended set of claims. Said claims are allowable under the demands of Article 19(2) and 34(2) PCT.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

- D1: DATABASE EMBL [Online] 294800 bp DNA linear, 5 July 2001 (2001-07-05)
CAPELA D ET AL.: 'Sinorhizobium meliloti 1021 complete chromosome; segment 8/12' Database accession no. AL591789 XP002271918 cited in the application -&
CAPELA D. ET AL.: 'Analysis of the chromosome sequence of the legume symbiont Sinorhizobium meliloti strain 1021' PNAS USA, vol. 98, no. 17, 14 August 2001 (2001-08-14), pages 9877-9882, XP002271919
- D2: FR-A-2 780 733 (GIST BROCADES BV) 7 January 2000 (2000-01-07)

novelty

The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1-9 is new in the sense of Article 33(2) PCT.

D1 discloses a genomic polynucleotide sequence of *Sinorhizobium meliloti* which comprises a segment with 86.36% identity (86.36% ungapped) in a 1019 nucleotide overlap (288-1306:69861-70879). Said segment encodes a polypeptide (also disclosed) with 93.7% identity (93.7% ungapped) in a 334 amino acid overlap (1-334:1-334). The function of said polypeptide is described as a putative transcription regulator protein. This particular polypeptide is considered as the orthologue of the disclosed sequence and will have the "activity of the transcriptional activator CobR". However, the presently claimed subject-matter excludes said polynucleotide and polypeptide sequence. Therefore, the subject-matter of claims 1-9 is new.

inventive step

Present claim 1 is directed to a process for the biological production of cobalamin using a DNA molecule (introduced in an appropriate host cell) which encodes a transcriptional activator for genes involved in vitamin B12 synthesis.

Closest prior art is D2. D2 discloses a process for the biological production of cobalmin which comprises introducing isolated DNA of plasmid p545 and growth under appropriate conditions to obtain production of cobalmin. Difference with the present claim 5 is the particular CobR sequence introduced in the host cells.

The problem to be solved is defined as the provision of an alternative process for the fermentive production of cobalmin by transformed host cells.

The solution proposed in claim 1 is considered as involving an inventive step for the following reasons: There is no incentive in the prior art that the sequence designated CobR, or any orthologous sequence, has an effect on the cobalmin synthesis. Hence, the subject-matter of claims 1-4 has an inventive step, under Article 33(2) PCT.

With respect to the subject-matter of claims 5-9, document D1 represents the most relevant state of the art. D1 discloses a genomic sequence encoding a putative transcriptional activator from *Sinorhizobium meliloti*, from which the subject-matter of claim 5 differs in that it is directed to the *Pseudomonas denitrificans* orthologue and closely related sequences which have a transcriptional activating effect on genes involved in vitamin B12 synthesis.

The problem to be solved may therefore be regarded as the provision of sequences orthologous to the *Sinorhizobium meliloti* putative transcription activator.

The solution proposed in claim 5 is considered as involving an inventive step for the following reasons:

The disclosed function of the polypeptide sequence in D1 as a putative transcription activator is so speculative, vague and broad that a skilled person has no incentive to isolate related sequences. Furthermore, he has no clue whatsoever neither from D1, nor from his knowledge as a skilled person or other prior art, that said sequence might function as an activator of transcription of genes involved in the vitamin B12 synthesis. Hence, presence of inventive step is acknowledged for claims 5-9,

Industrial application

The subject-matter of claims 1-9 has industrial applicability.

Re Item VIII

Certain observations on the international application

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Claims 1 and 5 refer to DNA sequences with preferable activities. Said wording does not present any limitation to the claimed subject-matter and is considered as enterly optional.